PCT / SE 2004 / 000817

2004-05-27

INVESTOR IN PEOPLE

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NP10 8QQ

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Dated 14 APR 2004

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P01/7700 0.00-0312321.3

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
K
29 MAY 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

29 MAY 2003

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

101097

2. Patent application number
(The Patent Office will fill in this part)

0312321.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ASTRAZENECA AKTIEBOLAG
S-15185 SÖDERTÄLJE
SWEDEN

Patents ADP number *(if you know it)*

08185217001

If the applicant is a corporate body, give the country/state of its incorporation

SWEDEN

4. Title of the invention

NEW COMBINATION

5. Name of your agent *(if you have one)*

ANNA GRIFFITHS-JOHNSON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ASTRAZENECA
GLOBAL INTELLECTUAL PROPER
48 CURZON STREET
LONDON W1J 7UL

08194045001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	15
Claim(s)	5
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Anna Griffiths-Johnson Date 29 May 2003

12. Name and daytime telephone number of person to contact in the United Kingdom ANNA GRIFFITHS-JOHNSON 020 7318 772

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

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NEW COMBINATION

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially rheumatoid arthritis.

Chronic inflammatory disorders such as rheumatoid arthritis are polygenic, highly complex, and involve multiple inflammatory and immune mechanisms. Treatment of these disorders has been largely empirical with a variety of therapeutic agents being used with little understanding of the mechanisms involved. Recent research suggests that two inflammatory mediators, the cytokines IL-1 and TNFalpha (TNFα), may play key roles in the inflammatory process in rheumatoid arthritis.

It would be desirable to develop new pharmaceuticals for use in treating inflammatory conditions/disorders.

In accordance with the present invention, there is provided a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The $P2X_7$ receptor (previously known as P2Z receptor) is a ligand-gated ion channel that is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular

adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1β (IL-1β).

An antagonist of the $P2X_7$ receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the $P2X_7$ receptor.

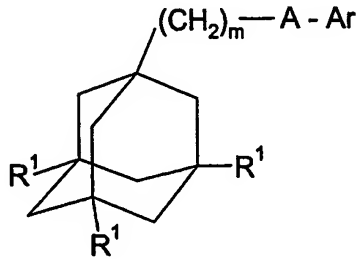
Methods for assaying for $P2X_7$ receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the $P2X_7$ receptor is activated using a receptor agonist in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Thus, an increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound or substance on the $P2X_7$ receptor.

In WO 01/42194, the assay is carried out by taking a 96-well flat bottomed microtitre plate and filling the wells with 250 μl of test solution comprising 200 μl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 μl of a high potassium buffer solution containing 10^{-5}M benzoylbenzoyl adenosine triphosphate (bbATP, a known $P2X_7$ receptor agonist), and 25 μl of the high potassium buffer solution containing 3×10^{-5}M test compound. The plate is covered with a plastics sheet and incubated at 37 °C for one hour. The plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) are used separately in the test as controls. From the readings obtained, a pIC_{50} figure is calculated for the test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. A pIC_{50} figure greater than 5.5 is normally indicative of an antagonist.

Examples of $P2X_7$ receptor antagonists include the compounds described in WO 00/61569, WO 01/42194, WO 01/44170 and International Patent Application No. PCT/SE02/02057

filed on 12 November 2002, the entire contents of which are incorporated herein by reference.

More specifically, WO 00/61569 discloses a compound of formula



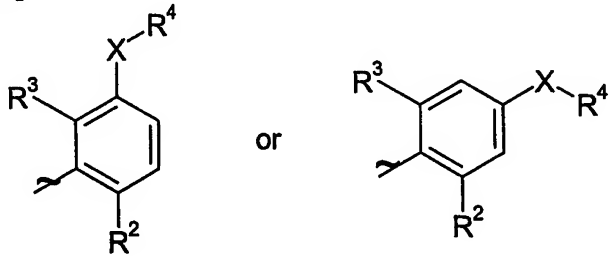
(I)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group



;

X represents a bond, an oxygen atom or a group CO, $(CH_2)_{1-6}$, CH=, $(CH_2)_{1-6}O$, $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, CR'(OH), $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $NR^5(CH_2)_{1-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$, $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$, $NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$, $CONR^5$, NR^5CO, $S(O)_n$, $S(O)_nCH_2$, $CH_2S(O)_n$, SO_2NR^5 or NR^5SO_2;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C_1-C_6 alkyl group;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one C_3-C_6 cycloalkyl, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkyloxy optionally substituted by at least one

C_3-C_6 cycloalkyl, and (iv) C_3-C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

either R^4 represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl;

r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1-C_6 alkyl or C_3-C_8 cycloalkyl group;

R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A represents C(O)NH and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(b) when A represents C(O)NH and X represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

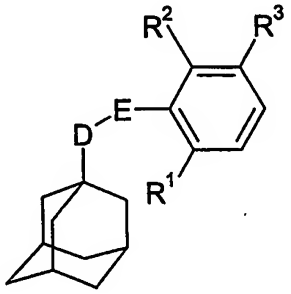
(c) when A represents NHC(O) and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(d) when A represents NHC(O) and X represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2, then R^4 does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^4 does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

WO 01/42194 discloses a compound of formula



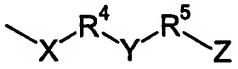
(I)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula



(II);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NR^{11}, SO or SO_2;

Z represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group;

R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

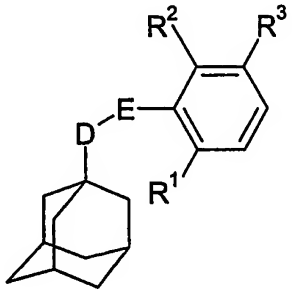
R^{11} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

WO 01/44170 discloses a compound of formula



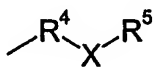
(I)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent hydrogen, halogen, amino, nitro, C_1-C_6 alkyl or trifluoromethyl, but R^1 and R^2 may not both simultaneously represent hydrogen;

R^3 represents a group of formula

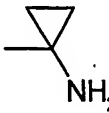


(II);

R^4 represents a C_1-C_6 alkyl group;

X represents an oxygen or sulphur atom or a group NR^{13}, SO or SO_2;

R^5 represents hydrogen, or R^5 represents C_1-C_6 alkyl or C_2-C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C_1-C_6-alkylamino, -Y-R^6,



, and

a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_6 alkyl;

Y represents an oxygen or sulphur atom or a group NH, SO or SO_2;

R^6 represents a group -R^7Z where R^7 represents a C_2-C_6 alkyl group and Z represents an -OH, -CO_2H, -NR^8R^9, -C(O)$NR^{10}R^{11}$ or -$N(R^{12})$C(O)-C_1-C_6 alkyl group, and, in the case where Y represents an oxygen or sulphur atom or a group NH, R^6 additionally represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, -C(O)$NR^{14}R^{15}$, -CH_2OC(O)R^{16}, -CH_2OC(O)OR^{17} or -C(O)OCH_2OR^{18};

R^8, R^9, R^{10}, R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

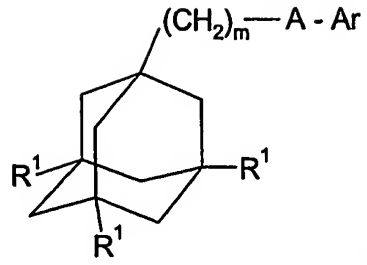
R^{13} represents hydrogen, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylmethyl, or R^{13} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represent a C_1-C_6 alkyl group;

with the proviso that when E is C(O)NH, X is O, NH or N(C_1-C_6 alkyl), then R^5 is other than a hydrogen atom or an unsubstituted C_1-C_6 alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

International Patent Application No. PCT/SE02/02057 discloses a compound of formula



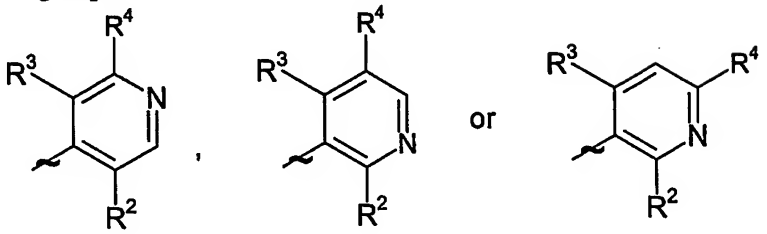
(I)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group

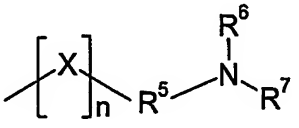


(II) (III) (IV)

;

one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3-C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

R^4 represents a group



(V);

X represents an oxygen or sulphur atom or a group >N-R^8;

n is 0 or 1;

R^5 represents a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

R^6 and R^7 each independently represent a hydrogen atom, C_1-C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1-C_6 alkoxy, and

(di)-C_1-C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3-C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy); and

R^8 represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

with the provisos that:

(a) when n is 0, then A is NHC(O), and

(b) when n is 1, X represents oxygen and A is C(O)NH, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl; and

(c) when n is 1, X is oxygen, sulphur or >NH and A is NHC(O), then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl or $-CH_2CH_2OH$;

or a pharmaceutically acceptable salt or solvate thereof.

In an embodiment of the invention, the $P2X_7$ receptor antagonist is

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-{[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl)nicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{[(2*S*)-2-hydroxypropyl]amino}propyl)isonicotinamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate,

ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like.

Examples of pharmaceutically acceptable solvates include hydrates.

The $P2X_7$ receptor antagonist used in the present invention may be capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the active ingredient and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

A tumour necrosis factor α (TNFα) inhibitor is a compound or other substance that is capable of inhibiting TNFα activity, whether fully or partially. Thus, the inhibitor may bind TNFα and includes anti-TNFα antibodies (such as "Remicade" (Infliximab) and "Humira" (D2E7) monoclonal antibodies) and receptor molecules which bind specifically to TNFα (such as "Enbrel" (Etanercept) fusion protein). In another aspect, the inhibitor may bind the TNFα receptor and includes anti-TNFα receptor antibodies. A detailed description of compounds or substances that may be used in the present invention as TNFα inhibitors can be found, for example, in published International patent application no. WO 98/05357, the entire contents of which are incorporated herein by reference.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as rheumatoid arthritis.

The first and second active ingredients are administered simultaneously (other than in admixture), sequentially or separately to treat inflammatory conditions. By sequential is meant that the first and second active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The first and second active ingredients are conveniently administered by oral or parenteral (e.g. intravenous, subcutaneous or intramuscular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

Oral administration of the first active ingredient is preferred, whilst parenteral administration of the second active ingredient is preferred.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the condition or disorder indicated. However, in general, satisfactory results will be obtained when the total, combined, daily dosage of first and second active ingredients is in the range from 10 to 2000 milligrammes (mg), particularly from 10, 20, 30, 40, 50, 100, 150, 200 or 300 to 1800, 1500, 1200, 1000, 800, 600, 500 or 400 mg.

The pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The present invention further provides the use of a pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:
(a) a (therapeutically effective) dose of a first active ingredient which is a $P2X_7$ receptor antagonist; and
(b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor,
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The present invention will now be further understood by reference to the following illustrative examples.

Example 1

Pharmacological analysis to determine the effect of TNFα inhibitor / $P2X_7$ antagonist combinations (without addition of a $P2X_7$ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysacharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. TNFα inhibitor and / or a $P2X_7$ antagonist or vehicle was then added to the cells. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNFα and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the presence of TNFα inhibitor alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with TNFα inhibitor were determined. The effects of the antagonists / TNFα inhibitor alone and in combination were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNFα) or on multiple mediators by $P2X_7$ antagonist / TNFα inhibitor combinations, in comparison to that achieved by either a $P2X_7$ antagonist or TNFα inhibitor alone, is an indicator for increased efficacy in the treatment of disease.

Example 2

Pharmacological analysis to determine the effect of TNFα inhibitor / $P2X_7$ anatagonist combinations (with addition of a $P2X_7$ agonist).

Human peripheral blood monocytes were prepared from the blood of healthy human volunteers collected in EDTA blood tubes. Monocytes were isolated by serial gradient centrifugation and washing to produce a pure population of cells. Lipopolysacharide (LPS) was then added to the cell suspension in tissue culture and this was incubated for 4 - 12 hours at 37 degrees centigrade. Test mixtures were then added followed by the addition of the $P2X_7$ receptor agonist BzATP. Test mixtures can comprise of vehicle as control, a $P2X_7$ receptor antagonist, or a combination of a $P2X_7$ receptor antagonist

together with TNFα inhibitor. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatants by specific ELISA assays for the cytokines IL-1, IL-18, TNFα and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with TNFα inhibitor were determined. The effects produced by a $P2X_7$ antagonist alone and in combination with TNFα inhibitor were then compared. Statistically significant levels of inhibitory activity against a single mediator (IL-1 or TNFα) or on multiple mediators by $P2X_7$ antagonist / TNFα inhibitor combinations in comparison to that achieved by a $P2X_7$ antagonist alone is an indicator for increased efficacy in the treatment of disease.

CLAIMS

1. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, for simultaneous, sequential or separate use in therapy.

2. A product according to claim 1, wherein the $P2X_7$ receptor antagonist is an adamantyl derivative.

3. A product according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-{[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl)nicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{[(2*S*)-2-hydroxypropyl]amino}propyl)isonicotinamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

4. A product according to any one of claims 1 to 3, wherein the second active ingredient binds TNFα.

5. A product according to claim 4, wherein the second active ingredient is an anti-TNFα antibody.

6. A product according to claim 4, wherein the second active ingredient is selected from Infliximab, D2E7 and Etanercept.

7. A kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is a tumour necrosis factor α

(TNFα) inhibitor, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

8. A kit according to claim 7, wherein the $P2X_7$ receptor antagonist is an adamantyl derivative.

9. A kit according to claim 7 or claim 8, wherein the $P2X_7$ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-{[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl)nicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{[(2*S*)-2-hydroxypropyl]amino}propyl)isonicotinamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

10. A kit according to any one of claims 7 to 9, wherein the second active ingredient binds TNFα.

11. A kit according to claim 10, wherein the second active ingredient is an anti-TNFα antibody.

12. A kit according to claim 10, wherein the second active ingredient is selected from Infliximab, D2E7 and Etanercept.

13. Use of a pharmaceutical product or kit according to any one of the preceding claims in the manufacture of a medicament for the treatment of an inflammatory disorder.

14. Use according to claim 13, wherein the inflammatory disorder is rheumatoid arthritis.

15. A method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is a $P2X_7$ receptor antagonist; and

(b) a (therapeutically effective) dose of a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor,

to a patient in need thereof.

16. A method according to claim 15, wherein the inflammatory disorder is rheumatoid arthritis.

ABSTRACT

NEW COMBINATION

The invention provides a pharmaceutical product or kit comprising a first active ingredient which is a $P2X_7$ receptor antagonist and a second active ingredient which is a tumour necrosis factor α (TNFα) inhibitor, for use in the treatment of inflammatory disorders.